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Helena Margarida Cruz Gens

CCR na mulher grávida

CRC in pregnant women

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CCR na mulher grávida / CRC in pregnant women

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CCR na mulher grávida
CRC in pregnant women

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Abstract

Background

Colorectal cancer in pregnancy is a rare pathology with limited high-grade evidence available for guidance. The diagnosis of CRC in pregnant women is usually delayed, and once diagnosis is made, challenges exist as treatment options may be limited.

Objective

The study aims to highlight the importance of early investigation of symptomatic patients during pregnancy, as well as to update treatment and prognosis in CRC.

Methods

A literature search in Pubmed database, including articles from 2006 to 2016 and cross-research articles with the initial research.

Results

Pregnancy can limit and contraindicate the utilization of standard diagnostic and therapeutic tools, which in particular can hamper the liberal use of colonoscopy and CT. Physical evaluation and abdominal US are first recommended; besides, MRI or CT may be used, only in indicated cases.

Surgery is the main stay of treatment but radiotherapy and chemotherapy have significant role in posterior management of tumour.

Discussion

As abdominal symptoms are common in pregnancy and colorectal cancer can simulate them, the differential diagnosis between these two pathologies is crucial, since early interventions can be curative.

After diagnosis, the follow-up of pregnant women should be individualized, depending on several factors. However, since cancer treatment is currently possible in pregnancy, the patient's survival probability should not be decreased due to late diagnosis.

Conclusions

Many studies are needed in order to achieve development in CRC pathogenesis during pregnancy as well as in treatment outcomes.

The potential curative treatment of the disease should be the main aim of treatment when considering CRC in pregnancy. However, it is crucial to adapt the treatment to each patient, taking into account conscious decision on pregnancy further management.

Resumo

Introdução

O cancro colorretal na gravidez é uma patologia rara, com limitada evidência científica para orientação terapêutica. O diagnóstico de cancro coloretal em mulheres grávidas é tardio e, quando o diagnóstico é feito, as opções de tratamento podem ser limitadas.

Objetivo

O objetivo deste estudo é ressalvar a importância da investigação precoce de pacientes sintomáticas durante a gravidez, assim como avaliar os atuais métodos de tratamento e prognóstico no CCR.

Métodos

A pesquisa bibliográfica foi realizada na base de dados PubMed, incluindo artigos a partir de 2006 até 2016, assim como artigos de pesquisa cruzada com os artigos iniciais.

Resultados

A gravidez pode limitar e contra-indicar a utilização de ferramentas de diagnóstico e terapêuticas convencionais, assim como dificultar o uso indiscriminado de colonoscopia e tomografia computadorizada. A avaliação física e a ecografia abdominal são a primeira linha para diagnóstico. No entanto, em casos selecionados, a ressonância magnética ou a tomografia computadorizada também podem ser usadas.

A cirurgia é o *gold-standard,* mas a radioterapia e a quimioterapia assumem um papel cada vez mais relevante no tratamento multidisciplinar destes tumores.

Discussão

Como os sintomas abdominais são comuns na gravidez e o cancro coloretal pode simulá-los, o diagnóstico diferencial entre estas duas patologias é crucial, já que intervenções precoces podem ser curativas.

Após diagnóstico, o seguimento das grávidas deve ser individualizado, dependendo de vários fatores. Porém, já que atualmente o tratamento do cancro é possível na gravidez, a probabilidade de sobrevivência da paciente não deve ser diminuída devido ao diagnóstico tardio.

Conclusões

Outros estudos são ainda necessários para saber mais acerca da patogénese do cancro coloretal na gravidez, assim como os resultados após tratamento.

O potencial objetivo é o tratamento oncológico do cancro coloretal. No entanto, é crucial adaptar o tratamento a cada paciente, tendo em conta a sua decisão consciente acerca da continuação da gravidez.

Key-words

Cancro do cólon; Cancro do reto; Gravidez; Diagnóstico do cancro; Tratamento do cancro.

Palavras chave

Colon cancer; Rectal cancer; Pregnancy; Cancer diagnosis; Cancer treatment.

Introduction

Background

Colorectal cancer (CRC) in pregnancy is a condition that represents a distinct entity from CRC in the general population, as it is a rare pathology with limited high-grade evidence available for guidance. In fact, the literature on this subject is scant with fewer than 300 cases reported(1), which means there is limited experience on the management of CRC diagnosed during pregnancy.

The diagnosis of CRC in pregnant women is usually delayed, because there is a significant overlap in signs and symptoms between a colorectal malignancy and normal pregnancy, impeding proper diagnosis(2–4). Once diagnosis is made, challenges exist as treatment options may be limited(2). That is why management requires judiciously individualized strategies after thorough patient counselling to deal with consequent emotional and physical stress, in order to ensure adequate psychological support and realistic expectations(2,5).

The primary objective of this review was to highlight the importance of early investigation of symptomatic patients during pregnancy, as well as the role of chemotherapeutic, radiological and surgical interventions. Secondary objectives include a research about epidemiology of CRC during pregnancy, its implications and prognostic features.

Methods

The literature survey was conducted in Pubmed database. The words "colon pregnancy cancer" and "rectum pregnancy cancer" were used. Only the articles published from 2006 to 2016 were considered. After reading the title and abstract, and subject to an availability of the article, 31 articles were obtained in Pubmed. Articles obtained by cross-searching with the articles of the initial research with relevant information were also added.

Results

Epidemiology

CRC is the third most common type of cancer in women(4) with its highest incidence occurring in patients aged 50 years old(6); women older than 40 years tend to be 11 times more likely to develop CRC than those younger than 30 years of age(7,8).

While the overall incidence of CRC is steady or falling, some studies report an increased incidence of CRC in younger patients (< 40 years)(1), which means that 3% of patients with this cancer are younger than 40 years old(6). Nevertheless, for this age group, studies report that overall survival of CRC for women has improved substantially, with 5-year overall survival now approaching 80%(9).

Because of the increase in the incidence of CRC in younger patients, it may occur during the reproductive age, interfering with pregnancy(1). Cruveilhier reported the first case of rectal carcinoma in pregnancy in 1842, but now it is the seventh most common type of cancer in pregnancy(5,6). However, its incidence rate is controversial; some studies report an incidence of 0,002%(3,4,6–8,10,11) while others consider 0.07% to 0,1%(12–14), which means about 1 case per 13.000 gestations(3,5,15). The mean age of women with CRC during pregnancy has been reported as 31 years of age(4–6,16),

with range of 16-48 years(12).

Considering racial predisposition, hispanic women were slightly less likely to develop CRC, in comparison with non-hispanic white women(8).

Most of CRC in pregnancy is an aggressive mucinous subtype(8), which have poorer prognosis(17), but primary signet-cell carcinoma (SRCC) of the colon and rectum also represents a form of adenocarcinoma of the large intestine. Although its rare incidence of about less than 0,1% of cases of CRC in pregnancy, patients with SRCC are younger(14).

Etiology and pathogenesis of CRC in pregnancy

CRC is one of the three most common types of cancer in women and can present in women of childbearing age, especially if there is a genetic predisposition(12).

In fact, environmental factors play a dominant role in the etiology of most CRC but inherited genetic factors are also significant in between 15% and 30% of cases. In about 5% of all cases, CRC is associated with a highly penetrant dominant or recessive inherited syndrome(18). When considering familial clustering of CRC and endometrial cancers, it is important to consider Lynch's syndrome (hereditary non-polyposis colorectal cancer (HNPCC)), as a cause of cancer in pregnant women(19). It is an autossomic dominant inherited genetic disease(20), and thus multiple generations can develop CRC at an early age (mean, 45 years). Lynch syndrome is likely if a family history meets the Modified Amsterdam Criteria or revised Bethesda guidelines(11)

Familial adenomatous polyposis (FAP) is another inherited syndrome, responsible for <1% of all CRC cases. FAP is transmitted as an autosomal dominant trait, and is caused by truncating mutations in the (**APC**) adenomatosis polyposis coli gene. Recently, the **MUTYH** (mutY homologue (**Escherichia coli**)) gene has been identified as a further polyposis gene, displaying an autosomal recessive pattern of inheritance(18).

In what concerns to environmental factors, delayed childbearing and increased maternal age may lead to an increased incidence of CRC complicating pregnancy(6,21).

Some investigators demonstrated that 20 to 54% of colon cancers have estrogen receptors (Ers), whereas others have demonstrated progesterone receptors (PgRs), which may be stimulated by the estrogen and progesterone produced during pregnancy. The role of these hormones in the etiology and progression of CRC are limited and conflicting(12), In fact, CRC pathogenesis and its relation to pregnancy is not well understood(8,12,17), and studies show that parity is not positively neither negatively associated with CRC(8).

When discovered during pregnancy, two-thirds of CCR in pregnant women tend to involve the rectum and sigmoid colon, unlike the general population where two-thirds arise from the extra pelvic colon(4,12–14,17). In fact, it is was reported that about 85% of CRC in pregnancy are below the peritoneal reflection(1,5,12,16).

Prevention and screening

Advances in molecular basis of CRC include identifying the adenomatous polyposis coli (APC) gene, P^{53} gene, mismatch repair genes, and loss of allelic heterozygosity.(17)

Accordingly, as familial adenomatous polyposis (PAF) is a known risk factor for CRC during pregnancy, patients with family history of HNPCC should perform genetic testing(1,5).

When a patient develop CRC at a young age, it is important to consider the possibility of a hereditary cause, so we should confirm her family medical history in what concerns to cancers. Identification of the germline mutation in a Lynch syndrome family allows their inclusion in lifesaving cancer surveillance programs, which has been proven to reduce CRC mortality(22). Therefore, screening tests should be performed on tumour tissues to help determine the likelihood of this condition and microsatellite instability (MSI) analysis is the first approach to identify patients with Lynch syndrome. Germline testing for mismatch repair (MMR) gene alterations should be performed(11), as an autosomal dominant MMR deficiency leading to a tumour with MSI was assumed to be the primary mechanism for Lynch syndrome(23). In fact, germline mutations in the genes MLH1, MLH2, MSH6 and PMS2 can lead to the development of the syndrome, and heterozygosity for a mutation in one of these genes can result in increased susceptibility to cancer(11).

If Lynch syndrome had been suspected early diagnosis is essential. The American Cancer Society guidelines recommend colonoscopy beginning at an earlier age for high-risk individuals(11,24). Periodic examination by colonoscopy leads to the detection of CRC at an earlier stage, to a 63% reduction of the risk of CRC and to a significant reduction of the mortality associated(25). Annual colonoscopy programs performed at the age of 25 years in patients with families that have at least 3 relatives with a history of CRC or other HNPCC-related tumours and in families with identified MMR defect(18). It is recommended a 3-year gap between colonoscopies because this time interval has proven effective for the detection of this condition(11).

When pregnant women with SRCC are analysed for microsatellite instability, studies confirm they represent about 30% of tumours. Moreover, mutations of K-ras and P^{53} gene have been reported in SRCC. Furthermore, replications of DNA are also suggested to be at least partly involved in carcinogenesis of SRCC(14).

Note down that genetic testing is only recommended for those with a family history suggestive of Lynch syndrome or other hereditary pattern, as most CRC are sporadic(11).

Clinical features and Diagnosis

Diagnosis of CRC during pregnancy is challenging secondary to the difficulty in distinguishing pain of gynaecologic and GI origin(16,26), and the overlap in signs and symptoms of cancer and pregnancy(1–3,5,13,16). Consequently, usually there is a delay in diagnosis of CRC during pregnancy(4–7,10,12,26). Those signs and symptoms include nausea, vomiting, abdominal pain, weight loss, anemia, abdominal mass, rectal bleeding and altered bowel habits such as constipation.

Physiologic adaptations in pregnancy may also alter clinical presentations(12) so, high degree of suspicion if clinical features are suggestive of GI obstruction.(17)

However, sometimes there is no suspicion of CRC because its symptoms are absent(3) and foetal movements are normal(17). In fact, several studies reported that CRC can develop during pregnancy without presenting symptoms(6,7,27).

When considering SRCC, symptoms usually develop later, leading to the non-

detection of cancers limited to mucosa and sub-mucosa(14).

Palpable abdominal mass is a uncommon finding(17) but a common problem can be excluded with a careful anorectal exam(1), yielding 67-84% accuracy in staging rectal carcinomas(14).

Intestinal obstructions are extremely rare in pregnant women[(2)] but when present, exploratory laparotomy must be commenced(28), as prompt operative intervention maximizes outcome for both foetus and mother(3).

Haemorrhoids or anal fissure, common causes of rectal bleeding, should be evaluated, and rectal examination should be performed when a patient presents with a complaint of pain and/or rectal bleeding(6,13). Persistent anorectal bleeding or rectal passage of tissue at the time of delivery is an ominous sigh of CRC cancer and should be investigated(12).

If a patient starts to lose weight while pregnant, she should be evaluated for maternal and foetal etiologies. Persistent nausea or vomiting, specially in the third trimester, should also be evaluated further(6).

Above all, it is crucial to consider complaints that are specific, severe or perseverate(3,4).

The diagnosis of CRC in a non-pregnant patient entails the tumour marker serum carcinoembryonic antigen (CEA), toraco-abdomino-pelvic imaging, and endoscopy with biopsy.

- CEA

Evaluation of abnormal laboratory values is important to optimize patient diagnosis. CEA levels have been used during pregnancy for the diagnosis, monitoring and prognosis of CRC. Unfortunately, CEA levels tend to be normal or slightly elevated during pregnancy(14,16,17), and are not considered a useful screening tool due to their low sensivity and specificity(12).

- Colonoscopy

Colonoscopy is the gold standard to confirm diagnosis as it provides direct visualization, accurate determination of location, and the opportunity to obtain tumour tissue for pathological diagnosis of CRC(4,14). The American Society of Gastrointestinal Endoscopy indicate that an endoscopic intervention is safer than radiologically guided or surgical operations(1,5). However, pregnancy is a relative contraindication as this procedure may complicate pregnancy(4,12–14), due to the risk of foetal exposure to potential teratogenic medications, uteroplacental insufficiency with maternal hypoxia or hypotention, and the risk for placental abruption with the mechanical pressure to the uterus(1,2,5,12). Accordingly, it is advised that strong indication should be present to proceed with an endoscopy, it should be delayed until second trimester where possible(1,5), the procedure time must be minimized and the lowest possible dose of sedative medications should be used(2).

With informed patient approval, the procedure may be performed with possible reduction in risk with the use of meperidine, because of its safer foetal profile, maternal oxygen administration, and gentle abdominal compression(12,14).

Because most cases of CRC during pregnancy are rectal carcinomas, if the lesion is confined to the distal colon, a flexible rectosigmoidoscopy (preferably without sedation) may be performed, as an alternative to colonoscopy(1,5,12,13). These one could be delayed in order to look for synchronous lesions.

Staging

In the literature, most CRC are usually detected in its advanced stages, secondary to late diagnosis(3), during second or third trimester of pregnancy(6,12,13). A study that reviewed 41 patients with CRC during pregnancy observed that all patients had stage II or greater disease(12), while other refers that 60% are already diagnosed at stage III or IV(13). It corresponds to Dukes stage B or higher at presentation(4).

Staging is critical to ensure one is not dealing with advanced stage IV disease, as local management of colorectal malignancy would change considerably(2).

- CT scan

Imaging evaluation during pregnancy is difficult since toraco-abdomino-pelvic CT scan, is relatively contraindicated in pregnancy. This procedure should be avoided particularly in the first trimester, secondary to the foetal risk of radiation exposure teratogenicity and carcinogenicity(2–4,12–14,17). However, it is suggested that risk of adverse foetal effects is very low at doses of radiation used for diagnostic purposes, so CT of pelvis and abdomen can be performed with minimal risk(2,28).

- Ultrasound

Ultrasound (US) evaluation is a reasonable alternative to CT. (17) It is especially useful for detection of hepatic metastases (2) (75% of sensitivity)(12,14) but, because of the gravid uterus, it has limited accuracy in detecting colon and rectal masses (3,12,13). Further diagnostics are frequently necessary when ultrasounds are negative.(3)

Transrectal ultrasound is helpful in late pregnancy to determine rectal cancer location and is more accurate in staging rectal cancer preoperatively, although it has not been proven to prolong survival.(17)

- MRI

Similarly, magnetic resonance imaging (MRI) is relatively safe in pregnancy and should be considered after US indeterminate findings (28), but is good practice to avoid non-urgent MRI, particularly in the first trimester. (1,2) Moreover, it should be performed without contrast (3) because contrasts have not been approved for the foetus (12,13), being gadolinium known as teratogenic agent. (2)

Treatment

Treatment during pregnancy is another challenging issue; Walsh et al have proposed an algorithm to manage CRC diagnosed during pregnancy based on the gestational age of the foetus, foetal lung maturity, cancer stage, need for adjuvant chemotherapy, and if elective or emergent surgery is indicated.(1,5,6,12,14,15)

The treatment goal is to implement therapy as soon as possible for the mother, (6,13) and balance this with delivery of the foetus with optimal for neonatal outcome. (1,12,13,16)

Treatment modalities may include surgery, radiation therapy and chemotherapy, depending on the stage of the cancer.(6)

- Surgery

Surgery is the primary therapy for CRC outside of pregnancy (12,14) (8) In pregnant women with CRC it is recognized as safe and feasible (1) but its timing in a is a pivotal issue (2) so it should be considered on a case-by-case basis.

However, as the majority of CRC malignancies diagnosed in pregnancy occur below the peritoneal reflection, the level of technical difficulty associated with surgery is increased.(2)

If bowel obstruction develops during the pregnancy, a self-expanding metallic stent (SEMS) can be useful as it allows solving the acute condition, providing time to prepare the patient for surgery, thus reducing both post-surgical morbidity and mortality.(29)

Although no high-grade evidence exists regarding management of CRC in pregnancy, some clinical guidelines are reported in literature:

- If diagnosis is made in the first 20 weeks of pregnancy, treatment delay can lead to disease progression and compromise of mother's life. Therefore, the recommendation is discontinuation of the pregnancy, according mother's followed by early cancer treatment with surgical resection, as in non-pregnant patients. (2,13,14,16) However, controversia data regarding risk to the pregnancy with surgery, if imaging suggests that the tumour may be resected with clear margins, surgery might be an option. (2) In fact, low anterior or abdominoperineal resection has already been performed up to 20 weeks gestation without disturbance of the gravid uterus.(12) However, as CRC diagnosis is rarely made prior to 20 weeks of gestation, there is limited data on foetal outcome after surgical resection.(12)

- If colon cancer is diagnosed after 20 weeks gestation, surgery can be delayed until delivery, in order to save the foetus (5,13,14,16), although endangering the patient with significant risk of disease progression (3), due to the pro-angiogenic state of pregnancy.(2) The ultimate goal is to achieve foetal lung maturation (8,16); nevertheless, delivery may vary from 28 to 32 weeks gestation, based on multispecialty team decision.(2,6,12) After that, treatment of CRC should take place as in a non-pregnant patient.(2,14,15)

In both cases, the extent of resection is determined by tumour size, location, histologic grade and tumour extension into the colon wall and into adjacent tissue and organs.(14)

- Chemotherapy

The need for chemotherapy depends upon the final histology of the tumour (2), being considered in stage II with high risk of recurrence (14) and stage III when nodal involvement is present.(8)

As a large portion of patients are diagnosed in advanced stages, is common that neoadjuvant chamoradiation before surgical resection is needed in rectal cancer. (13) Adjuvant chemotherapy has been shown to improve the survival rate by 5 to 10% for stage II or III CRC, (12) but evidence shows that in pregnant women with metastic rectal cancer it might spare the foetus, but not cure the mothers. (13)

Moreover, pelvic radiation is not recommended during organogenesis, in the first trimester of pregnancy (5,15,16), as it is associated with lethal damage to the foetus, with embryonic or foetal death, malformation, and growth retardation. (13,15) Although some studies reported that chemotherapy should be given only after delivery, other ones suggest that chemotherapy can be administered in the second or the third trimesters with dose maternal/foetal surveillence. (1,5,15) The recommended therapeutic agent is 5-fluoruracil (5-FU), which is an inhibitor of DNA synthesis.(4) Although 5-FU is reported to be associated with low or no risk of adverse reproductive outcomes (9,10), some investigators have suggested a the possibility of spontaneous abortion (1,5) and teratogenicity associated with 5-FU (5,12,15,16)

Other new chemotherapeutic agents platinum-based like cisplatin and oxiliplatin are available but, according to the U. S. Food and Drug Administration, they are not recommended during pregnancy. (12,15,16)

The previous reasons could explain why women with pregnancy-associated CRC were less likely to undergo chemotherapy, in comparison to non-pregnant women in the same condition.(8)

It is also important to report that, considering Lynch syndrome, tumours with MSI were more responsive to adjuvant chemotherapy than tumours without MSI.(11)

- Radiotherapy

Adjuvant radiotherapy is indicated for Duke's B2 and C rectal cancers (12), T4 lesions adherent to the pelvic structure and in patients with close or positive surgical margins.(8,14) Nevertheless, radiation treatment of the pelvis is contraindicated during pregnancy (2,5,15) and is usually delayed until after delivery (12,16) as it has been implicated in sexual and gonadal dysfunction, foetal growth restriction or spontaneous miscarriage. (9)

- Biological therapies

Biological agents like bevacizumab, cetuximab or panitumumab provide relatively modest survival increase in addition to standard chemotherapy, withholding their use until delivery would not be likely to prevent curative treatment.(10)

In stage IV disease, palliative management should be performed and emphasis should be to lengthen the progression-free and overall survival in the unresecable metastic CRC. (14)

(12)

Vaginal delivery vs cesarean

The delivery mode is controversial as cancer per si is not an indication to perform a cesarean section. (5,16) However studies show that cesarean section is more practiced in women with pregnancy associated with CRC.(8)

Outside the normal obstetrical indications for cesarean section, indications for an operative delivery in CRC patients include a tumour along the anterior rectal wall, secondary to increased risk of bleeding with vaginal birth pressure or birth canal obstruction by tumour.(12) Cesarean also can be considered if resection of the CRC at the time of delivery will be performed.(5,14,16)

There has been a recent move toward vaginal delivery for women with rectal carcinoma, even with an unripe cervix requiring a cervical ripening agent. (12)

Complications

The delay in diagnosis lead to an increase of complications as the uterus, cervix and adnexa share the same visceral innervation as the lower ileum, sigmoid colon, and rectum. (26) About 25% of pregnant women with CRC will have ovarian metastases. (12,14,16) If tumor resection is performed during pregnancy, prophylactic ovarian removal may be deferred secondary to the possible risk for a spontaneous abortion, especially in the first trimester. Bilateral oophorotomy is performed during pregnancy, if evidence of invasion. (12,16)

The liver is the most common site for synchronous metastases (14) but there are no reports of liver resection for CRC liver metastases during pregnancy.(10,16)

Colon obstruction, perforation, and metastasis are more frequent in pregnant women with CRC than the average population, (17) possibly due to the immunosuppressive state of pregnancy.(12)

Foetal risk

Its reported that higher rates of preterm labour and major puerperal infections are noted in women with pregnancy associated with CRC, as this malignant condition prone to infections that may be sub-clinical before delivery. (8) This could be explained by the malignancy-related immune suppression, as CRC initiates an inflammatory reaction that consequently starts the preterm labour cascade secondarily to the close proximity to the uterus.(8)

Despite high rates of preterm delivery, some studies reported an absence of adverse foetal outcomes (5,8), while others refer that only 78% of foetus from women with CRC survived.(5) Conversely, there is agreement that the risk of foetal malignancy is rarely observed, even when the disease is in an advanced stage with widespread metastasis. (5,17) However, metastasis to the placenta was reported once in maternal colorectal malignancy.

Even though a complete evaluation of the placenta is recommended, there is no evidence to support periodic follow-up of the baby.(5)

Prognosis

Pregnant women with CRC tend to have poor outcome, which usually includes widespread metastasis (5), mainly secondary to delayed diagnosis. (4,6,8,12,16).

Moreover, when considering SRCC, it is more likely to experience lymph node metastasis, have an aggressive clinical course and poor prognosis. (14)

Previous studies reported that patients with CCR regarding Lynch syndrome with MSI survived longer than patients with non-MSI tumours did; accordingly, the former ones showed lower mortality rates when stratified by tumour stage, including patients with stage IV cancer.(11) Hence, the detection of MSI in a CCR is a positive prognostic factor, particularly among young patients.(11,20)

Most of all, it is important to notice that women that are not surgically treated died at a rate that was 4.2 times that of women who undergo surgical treatment.(8)

When comparing pregnant to non-pregnant women with CRC, 5 year cancer survival is the same (12) Women with colon cancer died at a faster rate than those with rectal or anal cancer, even though it is reported that pregnancy was not associated with a significant difference in survival between these two groups. (5,8)

Discussion

After this review it appears that there is still much to be clarified, especially in the treatment area. Despite a rising incidence of CRC in pregnancy due to, at least in part, more women falling pregnant at an advanced maternal age, only few studies were performed about this issue. Moreover, most of those have not been completed due to ethical reasons, so there is information evaluating new therapies.

CRC in pregnancy is rare but its incidence is increasing not only because more women are postponing pregnancy until later in life but also because there is an increased risk for this cancer in women with more than 40 years old.(5,10)

This cancer in gravidity is not well understood but, as genetic alterations contribute to the susceptibility to CRC it is important to offer genetic counselling, especially when other CRC is recognised in the family history.(8)

As abdominal symptoms are common in pregnancy and CRC can mimic them, they are overlooked. (6,13,16) Thus, differential diagnosis should include the patient's history, physical examination, laboratory data, and radiologic findings that may assist in identifying the diagnosis (12); an appropriate work-up may result in prompt evaluation, detection and appropriate interventions to treat CRC (6,12,28) as early diagnosis improves survival and treatment outcomes.(1,2,6) In the era of possible cancer treatment in pregnancy, patient's chance of survival should not be diminished by delayed diagnosis.(7)

Further management is individualized and dependent on various factors including maternal age, patient's desire for future fertility, gestational age at diagnosis, and cancer stage.(12) However, pregnancy can limit and contraindicate the utilization of standard diagnostic and therapeutic tools due to a gravid uterus and a potentially vulnerable foetus, which can hamper the liberal use of colonoscopy and CT. (1,13) Physical evaluation plays an essential role, specially the evaluation of liver size and a rectal examination to screen for masses. (6) Abdominal US is first recommended, but its use is limited due to the patient's change in body habitus (28). MRI or CT may be used if necessary, although CT is not desirable due to foetal irradiation (28). Laparoscopy,

EGD, and sigmoidoscopy can be performed during pregnancy, when strongly indicated.(12)

Most medications appear to be relatively safe to the foetus and can be used when benefits to the mother outweigh potential foetal risks. (12)

Surgery is the main stay of treatment but its indications differ if CRC diagnostic occurs in the first half or in the second half of pregnancy. Secondarily, in adjuvant and neoadjuvant settings, RT and CRT have significant role in accordance to the site of tumor.(14) However, there is few data suggest association between pregnancy outcome and treatment with chemotherapeutic agents, used in treatment of CRC. (12) Therefore, it may still difficult to provide precise guidance to patients about long-term effects of this treatment. (9,16)

Conclusion

The coexistence of malignant tumour and pregnancy is a state of simultaneous occurrence of two completely contradictory phenomena – the development of a new life and a life-threatening terminal illness. In fact, CRC is an aggressive cancer that is rarely found during pregnancy, but when it appears it is expected poor outcome, as its usually diagnosed in late stages. (6,12,13)

Because there are no absolute guidelines, it is associated with diagnostic and therapeutic challenges,(10,13) as gravidity requires further quick and adequate diagnosis. (3)

There is necessary further investigations about diagnostic and treatment modalities with reduced foetal side effects, in order to diminish its incidence and mortality rate.(1) Follow-up of the infants in later childhood and adolescence as the central nervous system continue to develop, with additional reporting of cases, is needed to establish the safety of chemotherapeutic treatment of CRC during pregnancy.(16)

In fact, treatment during pregnancy varies widely and poses significant legal, ethical, religious, emotional and scientific challenges; therapy should be individualized and defined by a multidisciplinary team (12) that considers not only through patient counselling, but also the best management for both the patient and her foetus. (2) All the professionals who look after such a special patient should inform her considering the most current and reliable knowledge, providing her a multidisciplinary care, and understanding the complexity of coexistence of cancer and pregnancy. The patient should have the opportunity to decide about the fate of her pregnancy and it should not be affected by the moral beliefs of the doctor; the final decision concerns only to the patient(1,21,30,31)

Above all, the treatment strategy for CRC should be no different for pregnant and non-pregnant patients in terms of the aim, which is potential curative treatment of the disease, but should always consider the patient's conscious decision on pregnancy further management.

Conflict of interest

The authors have no commercial or other associations that might pose a conflict of interest in connection with the manuscript.

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ANEXO

The Journal of Coloproctology (JCOL) publish articles that contribute to the improvement and the development of the practice, research, and training in Coloproctology and related specialities. Also published in English version, starting in vol. 31, issue 3, 2011. The guidelines are based on the format proposed by the International Committee of Medical Journal Editors (ICMJE) and published in the article: Uniform requirements for manuscripts submitted to biomedical journals, wich was updated in April 2010 and is available on the Website (http://www.icmje.org).

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